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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/096,589	06/12/1998	ROBERT J. SCHNEIDER	5914-65	1985

20583 7590 10/01/2004

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
PROUTY, REBECCA E	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/096,589	SCHNEIDER ET AL.	
	Examiner	Art Unit	
	Rebecca E. Prouty	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *47-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *47-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 7/14/04 has been entered.

Claims 1-46 have been canceled. Claims 47-54 and newly presented claim 55 are still at issue and are present for examination.

Applicants' arguments filed on 7/14/04, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claims 47-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 47-50 and 55 are confusing in the recitation of a compound which "inhibits Src kinase activity that is enhanced in a cell infected with HBV relative to a same cell type not infected with HBV"... "with the proviso that if the compound is an antisense molecule, it is an antisense molecule to a Src kinase family member" as antisense oligonucleotides to Src kinase family members are not compounds which inhibit Src kinase activity that is enhanced in a cell infected with HBV relative to a same cell type not infected with HBV. Claims 51-54 are similarly confusing in the recitation of "a compound that inhibits activation of Src kinase"... "with the proviso that if the compound is an antisense molecule, it is an antisense molecule to a Src kinase family member" as antisense oligonucleotides to Src kinase family members are not compounds which inhibit Src kinase activation. As shown in the specification infection of a cell with HBV results in the activation of endogenous Src kinase, i.e., the conversion of inactive Src kinase to active Src kinase. Antisense oligonucleotides to Src kinase family members inhibit the **production** of the Src kinase family member by inhibiting either transcription and/or translation of the gene encoding the kinase. Such compounds have no effect on the activation state

of the kinase and thus are not within the scope of a compound which "inhibits Src kinase activity that is enhanced in a cell infected with HBV relative to a same cell type not infected with HBV" or "inhibits activation of Src kinase". As such the meaning of the claims is unclear. For purposes of examination it is assumed that the proviso excludes all antisense compounds.

Claim 49 is confusing in the recitation of "wherein reduced Src kinase activity in cells expressing HBX contacted with said compound as compared to cells expressing HBX not contacted with said compound indicates that enhanced Src kinase activity has been inhibited" as the indicated steps in no way lead to the ability to distinguish Src kinase activity that is enhanced in a cell infected with HBV relative to the same cell not infected with HBV (which is the intended result of the method recited in the preamble of the claim) from Src kinase activity that is endogenous to the cell as there is no step of comparing the effect of the compound on the Src kinase activity of cells not expressing HBx.

Claim 55 is confusing in the recitation "an antisense molecule to a Src kinase family member selected from the group consisting of antisense molecules to Ras, Raf, MAPK kinase C-Myc and cyclin-dependent kinase" because Ras, Raf, MAPK kinase C-Myc

and cyclin-dependent kinase are not Src kinase family members. Applicants are refered to page 8 of the specification which states "As used herein, the terms "Src kinase" or "Src kinase family" refer to the related homologs or analogs belonging to the mammalian family of Src kinases, including, for example, the widely expressed c-Src, Fyn, Yes and Lyn kinases and the hematopoietic-restricted kinases Hck, Fgr, Lck and Blk". The proteins listed are downstream components of the Src signaling cascade. It is further noted that antisense molecules to each of these downstream components of the Src signaling cascade are also not within the scope of compounds which "inhibits Src kinase activity that is enhanced in a cell infected with HBV relative to a same cell type not infected with HBV" as these proteins act downstream of Src kinase and thus have no effect on the activation state of Src kinase.

Claim 55 is further confusing in the recitation of "in which the compound" … is "a dominant negative mutant protein selected from at least one of Fyn, Ras, Raf, MAPK kinase, MAPK, and Myc dominant negative mutant proteins" as each of Ras, Raf, MAPK kinase, MAPK, and Myc are downstream components of the Src signaling cascade and thus have no effect on the activation state of Src kinase and Fyn is a Src kinase family member itself

and thus has no effect on the activation of Src kinases that results from HBV infection. Since each of the compounds listed in Claim 55 is outside the scope of the limitations of compounds defined by Claim 47 (from which Claim 55 depends), the meaning of this claims is so unclear that further examination is impossible. As such Claim 55 has been examined as a duplicate of Claim 47.

Claims 47-55 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of inhibiting HBV infection or replication by administering a compound that inhibits Src kinase activity that is enhanced in a cell infected with HBV relative to a same cell type not infected with HBV. As such the claims recite inhibiting proteins which participate in the conversion of inactive Src to active Src following infection with HBV. While at the time of filing of the instant application it was known that phosphorylation of Tyr-416 and/or dephosphorylation of Tyr-527 result in activation of Src kinase,

the proteins responsible for any such modification which occur in response to HBV infection were not known. The specification fails to describe in any fashion the physical and/or chemical properties or any identifying characteristics or properties other than the functionality of inhibiting enhanced activity of Src kinase resulting from the presence of HBV of the claimed class of substances and fails to identify even a single representative species of such compounds. Moreover, the specification fails to describe how the presence of HBV or HBx results in the activation of Src kinase such that the ordinary skilled artisan would have guidance regarding the types of compounds which should be investigated. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Applicants argue that page 12, lines 24-29 of the specification indicates that the present invention encompasses "methods and pharmaceutical compositions designed to target HBX mediated activation of Src kinase, members of the Src tyrosine kinase family and components of the Src kinase family signal

transduction pathway for the treatment of HBV infection". Applicants argue that a number of different protocols to inhibit HBV infection and/or replication are described including, but not limited to inhibition of essential activities of Src kinase activation associated with HBV infections and in particular the specification describes specific embodiments of the invention encompassing methods to inhibit HBV by inhibiting the Src family of kinases and to inhibit HBV by modulation of activation of the Src kinase signaling cascade. The examiner agrees with applicants that the specification indicates that multiple different methods of inhibiting HBV infection and replication are intended to be encompassed. However, these methods were restricted from each other and the current claims encompass only methods of inhibiting HBV infection and replication by inhibition of essential activities of Src kinase activation associated with HBV infections. Applicants argue that at page 13, lines 23-27, the specification teaches additional useful compounds for inhibiting activation of Src kinase including "dominant-negative mutants, SELEX RNAS, and antisense molecules targeted to Src kinase family members, Src-activated enzymes, downstream effectors of Src kinase and their signal transduction pathways". However it should be noted that the list applicants

are referring to includes compounds which inhibit activation of the Src kinase **signaling cascade** and thus include compounds which inhibit the activation of downstream components of the cascade. However, the current claims are limited to compounds which inhibit the **activation of Src kinase** only. Dominant-negative mutants, SELEX RNAS, and antisense molecules targeted to Src kinase family members, Src-activated enzymes, and downstream effectors of Src kinase would only inhibit activation of components of the cascade downstream from Src kinase. Compounds which inhibit the activation of Src kinase would include dominant-negative mutants, SELEX RNAS, and antisense molecules targeted to proteins of the Src kinase signaling cascade upstream of Src kinase itself (i.e., HBx) but the only protein known at the time of filing the instant application to be upstream of Src in the signaling cascade resulting from HBV infection is HBx. The specification makes it clear that while other proteins may be involved in the cascade between HBx and Src, the identities and functions of such proteins are unknown. Finally applicants argue that "In particular, compounds which may be used in accordance with the present invention to specifically target activation of Src kinase are binding proteins and competing ligands that prevent the intramolecular

interaction between the carboxy-terminal phosphorylated tyrosine residue and the SH2 domain located in the amino-terminal half of the molecule and the immediately adjacent SH3 domain." While the examiner agrees that such compounds would modulate the activation of Src kinase they would not be within the scope of the instant invention as proteins which prevent this interaction would be **activators** of Src kinase as the presence of the intramolecular interaction between the carboxy-terminal phosphorylated tyrosine residue and the SH2 domain located in the amino-terminal half of the molecule is well known in the art to maintain Src kinase in its inactive state. Applicants further go on to list a variety of know Src kinase enzymatic activity inhibitors and state that Exhibits A-C filed with the current response show that representative members of the Src kinase activation inhibitors taught as useful in the specification indeed phosphorylate Src kinase. However, it is not clear what portions of Exhibits A-C applicants are referring to as the Exhibits do not appear to the examiner to be relevant to compounds which phosphorylate Src. The specification describes all of these compounds as examples of Src kinase enzymatic activity inhibitors and **not** examples of inhibitors of Src kinase activation as induced by HBV and/or HBx. Thus the

specification does not describe these compounds as species within the currently claimed genus of compounds. While it was known in the art that one mechanism of Src kinase activation was the dephosphorylation of Y527 and/or the phosphorylation of Y416 and many tyrosine kinase and phosphatase inhibitors are known, there is no showing in the specification that HBV activation of Src kinase is achieved by either or both of these mechanisms and it is unclear what if any tyrosine kinase/tyrosine phosphatase should be inhibited in order to produce inhibition of Src kinase activation induced by HBV and/or HBx. It should be noted that any of known tyrosine kinase inhibitors which lack activity against the Src kinase itself might act as activators of HBV infection and replication (if they inhibit phosphorylation of the kinase which phosphorylates Y527) or inhibitors (if they inhibit the kinase which phosphorylates Y416) or have unpredictable effects (if they inhibit both the phosphorylation of Y527 and Y416). As the mechanism of HBV activation of Src kinase was not known in the art nor described in the specification, one of skill in the art would not have been in possession of knowledge of even a single compound which clearly falls within the scope of the currently claimed genus and even if applicants can show that one or more of the compounds

dislosed as Src kinase enzymatic activity inhibitors also falls within the currently claimed genus, the disclosure of only a single or a few species within the genus clearly would not be representative of the entire genus.

Claims 47-55 are further rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention because the proviso included within the amended claims is new matter.

The specification as filed does not suggest a genus of inhibitors of Src kinase activation that includes any compound with this function except for antisense molecules (or except for a specific subgenus of antisense molecules). The negative limitation in this claims is nowhere either explicitly nor implicitly found in the specification as filed.

The rejection of the claims under 35 U.S.C. 103(a) as being unpatentable over Moriya et al. is withdrawn in view of the limitation of the claims to exclude antisense molecules from the scope of the compounds used.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca Prouty, Ph.D. whose telephone number is (571) 272-0937. The examiner can normally be reached on Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Rebecca Prouty
Primary Examiner
Art Unit 1652